REMARKS

Claims 1-2 and 4 are pending in this application with claim 1 being the sole independent claim.

We note that the current Office Action indicates the prior docket number (i.e., 31755-A-PCT-USA-1). We would appreciate the Examiner's assistance in having the docketing number updated for this application to reflect our docketing number of 108140.00015. Your assistance is appreciated.

Rejection under 35 U.S.C. § 103(a)

Claims 1-2 and 4 stand rejected under 35 U.S.C. §103(a) as being unpatentable over the combination of Hirsch et al and Krska et al. Applicants respectfully traverse this rejection for the reasons of record and for the additional reasons set forth below.

The Presently-Claimed Invention

The presently-claimed invention relates, generally, to a method for identifying cellular protein antigens, to which a subject with cancer produces autoantibodies. The method consists of the following steps: (a) extracting proteins from a sample of cells; (b) separating the extracted proteins by two-dimensional electrophoresis; (c) transferring the proteins separated by two-dimensional electrophoresis to a membrane; (d) incubating the membrane with serum from a subject known to have the cancer; (e) detecting the proteins to which autoantibodies in the patients serum have bound; and (f) comparing the proteins to which antibodies in the subject's serum sample bind to proteins to which antibodies in control serum sample bind. Those proteins bound by antibodies in the subject's serum, but not the control serum, are identified as cellular protein antigens to which a subject with cancer produces autoantibodies.

Hirsch et al. and Krska et al.

Hirsch et al. is cited for disclosing a method of identifying proteins that induce antibodies in Hodgkin's disease (i.e., lymphoma) by isolating proteins from cancer cells derived from Hodgkin's disease patients and subjecting the isolated proteins to 2D PAGE followed by Western blot analysis with sera from cancer patients as compared to normal control patients.

The proteins bound by antibodies present in serum of cancer patients, but not in serum of normal patients, are identified as proteins to which a subject with cancer produces antibodies, and detecting the proteins to which the antibodies in the subject's serum sample have bound using an antibody that is specific for autoantibodies in the subject's serum sample.

In response to Applicants' previous arguments, the Office Action appears to take the position that Applicants' previously-submitted arguments that Hirsch et al. discounts various bands and spots as mere "background noise" are not correct. The Office Action indicates that one of skill in the art would conclude that only spots differing between test and control samples represent signal, and that by comparing the results, any "background noise" would be readily discernable.

The Office Action also takes the position that Hirsch et al. does not teach that any spots unrelated to proteins previously discovered by 1D Western blot are merely "the usual background." However, in response to this contention, Applicants submit that the Office Action has apparently not considered the legend to Figure 1a-c found at the bottom of page 205. It states: "[a] polypeptide with a molecular weight of $65x10^3$ daltons gave a strong reaction in the one- (B,C) and two-dimensional (A) blots. ***Additional faint bands and spots reflect the usual background reaction***." (Emphasis added) Applicants are at a loss to understand why this disclosure has not been taken into account in the Office Action.

Further, while it is apparent from Hirsch et al. that antibodies were produced for one protein, namely, P-65 in leukemia patients, Hirsch et al. first had to perform 1D PAGE and Western blotting to identify a protein to which only 17% of patients with cancer studied raise antibodies, and to which 2% of controls also have reactive antibodies. This lack of discrimination leads Hirsch et al. to conclude that "the relationship between antibodies to P-65 and HD is not clear" (p. 207, col. 1, lines 3-4).

One of ordinary skill in the art, having the disclosure of Hirsch et al. before him or her, would conclude that 2D Western blots may only be interpreted by having *a priori* knowledge of the protein of interest. The presently-claimed invention provides a means, previously not available, for performing 2D Western blots to discover proteins to which patients with cancer raise autoantibodies, where individuals without cancer do not, ***without prior knowledge of the proteins to be so identified***. By not dismissing spots as "the usual background" and by providing

a method of directly comparing the protein spots recognized by antibodies from cancer patients and cancer-free controls, the presently-claimed invention provides a method that is the exact opposite of that disclosed in Hirsch et al.

Krska et al. is cited for allegedly disclosing a conventional 2-D electrophoresis method for detecting primary antibodies bound to the antigen of interest that are transferred to a membrane. However, without conceding that the combination of Hirsch et al. and Krska et al. is proper, Applicants submit that Krska et al. does not remedy the deficiencies of Hirsch et al. with respect to the presently-claimed invention.

The Examiner has taken the view that Krska et al. provides further support for a method of 2-dimensional PAGE followed by Western blotting analysis. Applicants have not claimed such a method in isolation and acknowledge that the use of 2D gel separation followed by Western blotting was known to the skilled artisan prior to the date of the current invention. The key difference between the presently-claimed invention and the cited references is that Krska et al. and Hirsch et al. both require *a priori* knowledge of the protein of interest ***before*** the Western blot patterns can be interpreted, whereas the presently claimed invention permits the discovery of proteins ***without prior knowledge of the proteins to be so identified.***

Furthermore, Krska et al. does not use sera containing antibodies raised against endogenous antigens, but rather uses polyclonal and monoclonal antibodies artificially raised by immunization with the target protein. Even using this approach, Krska et al. teaches the necessity of testing antibodies for their ability to detect the denatured form of the target protein in Western blots (p. 6434, col. 1, line 46 – col. 2, line 1) before they can be used routinely. Using this approach, Krska et al. obtained only 1 out of 700 hybridoma clones with the required characteristics (p. 6435, col. 2, lines 28-37). In reviewing Krska et al., one of ordinary skill in the art would conclude that it was extremely unlikely that the natural presentation of an endogenous protein would elicit an antibody response capable of recognizing the denatured forms of proteins in Western blots. (This position is supported by the attached excerpt from Sambrook et al., Molecular Cloning: A Laboratory Manual, which was submitted in the recent opposition proceedings of the corresponding European application.)

The Office Action takes the position that one skilled in the art would combine the disclosures of Hirsch et al. and Krska et al. because their combined teachings provide the means and motivation to identify proteins to which a subject with cancer produces antibodies.

It must be understood that developing a Western blot with a serum sample from a cancer patient is very different from using a polyclonal hyperimmune serum from a rabbit, or a hybridoma culture supernatant containing a murine monoclonal antibody. The complexity of the staining pattern in the former case compared to the latter two situations renders interpretation difficult. When faced with such complexity, Hirsch et al. dismissed it as "the usual background staining." In consulting Krska et al., the skilled artisan would expect to see a very clean Western blot result with a single protein being visualized. As clearly demonstrated by the present invention, this is far from the case, and rather than representing "the usual background," the protein spots revealed by the presently-claimed method allows the identification of important cancer-associated antigens to which patients with cancer mount an antibody response, while subjects without cancer do not.

Taken together, Hirsch et al. and Krska et al. suggest that the prevalence of antibodies in the serum of cancer patients that react with cellular proteins derived from a host's tumor or representative thereof would be extremely low, if present at all. Furthermore, neither document teaches the identification of proteins to which patients with cancer have mounted a detectable antibody response while those without cancer do not, since even the control group in Hirsch et al. exhibits antibody reactivity to P-65.

The skilled artisan would thus lack the means and motivation to arrive at the present invention based on the combination of Hirsch et al. and Krska et al.

Accordingly, the combination of Hirsch et al. and Krska et al. fails to disclose or suggest all of the features of the claims, and nothing in their disclosures would lead one skilled in the art to modify them to arrive at the presently-claimed invention without the benefit of hindsight reconstruction based on Applicants' disclosure. Applicants therefore submit that claims 1-2 and 4 are patentable over the combination of Hirsch et al. and Krska et al., and respectfully request withdrawal of this rejection.

CONCLUSION

In view of the foregoing, reconsideration of the application, withdrawal of the outstanding rejections, allowance of claims 1-2 and 4, and the prompt issuance of a Notice of Allowance are respectfully requested.

Should the Examiner believe that anything further is necessary in order to place this application in better condition for allowance or that a telephone interview would expedite issuance, the Examiner is requested to contact the undersigned at the telephone number listed below.

In the event that any additional fees are needed for entry of this Response, the undersigned authorizes such fees to be charged to our Deposit Account No. 01-2300 referencing docket number **108140.00015**.

Dated: February 27, 2008 Respectfully submitted,

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